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(54)【発明の名称】　苦味剤を含有するガス組成物

(57)【要約】

【課題】　相当強い苦味を有する苦味剤を幻覚が起こるガスに含有させ、人や動物が直接あるいは間接的に吸引する場合には拒否感が生ずるガス組成物を提供する。

【解決手段】　ガス組成物は苦味剤を含有し、好ましくは、前記苦味剤を０．０５ｐｐｍ以上１０，０００ｐｐｍ以下で含有し、ガスは、炭素原子数が１～１０の炭化水素系のガスである。

【特許請求の範囲】

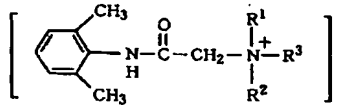
【請求項１】　苦味剤を含有することを特徴とするガス組成物。

【請求項２】　請求項１記載のガス組成物において、前記苦味剤を０．０５ｐｐｍ以上１０，０００ｐｐｍ以下で含有することを特徴とするガス組成物。

【請求項３】　請求項１記載のガス組成物において、ガスは炭素原子数が１ないし１０の炭化水素系のガスであることを特徴とするガス組成物。

【請求項４】　請求項１記載のガス組成物において、前記苦味剤はカシン、ケブラショ、クエルセチン、キニーネ、塩酸キニーネ、硫酸キニーネ、八アセチル化スクロース、安息香酸スクロース、ナリンギン、ブルシン、硫酸ブルシン、リモニン、ゲンチアナ紫、アガリシン酸、カフェイン、および次の構造式

【数１】

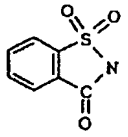


（Ⅰ）

（式中、

R^1 とR^2 は互いに同じかあるいは異なるもので、各々炭素原子数が１ないし４のアルキル基であり；R^3 はベンジル基あるいはクロロベンジル基であり；Ｘはハロゲン原子、RCO_2 （式中、Ｒは炭素原子数が１ないし６の直鎖状あるいは分鎖状のアルキル基、又はペニル基を示す）又は次の構造式

【数２】



（Ⅱ）

で表されるサッカリドを示す）で表されるｗ－ジアルキルアミノ－２，６－ジメチルアセトアニリドの第四級有機塩から成る群より選ばれる単独化合物あるいは２種以上の化合物の混合物であることを特徴とするガス組成物。

【請求項５】　苦味剤および苦味剤を溶解する溶媒を含有することを特徴とするガス組成物。

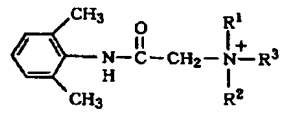
【請求項６】　請求項５記載のガス組成物において、前記苦味剤を溶解する溶媒は、ガス組成物全体に対して０．１重量%以上１０重量%以下で含有されることを特徴とするガス組成物。

【請求項７】　請求項５又は６記載のガス組成物において、前記苦味剤を溶解する溶媒は、炭素数が１以上の直鎖状、分鎖状あるいは環状のアルコール、アセトン、メチルエチルケトン、ベンゼン、トルエン、エチルアセテート、クロロホルム、ジクロロメタンおよびジエチルエーテルから成る群より選ばれる単独溶媒あるいは２種以上の混合溶媒であることを特徴とするガス組成物。

【請求項８】　請求項５記載のガス組成物において、ガスは炭素原子数が１ないし１０の炭化水素系のガスであることを特徴とするガス組成物。

【請求項９】　請求項５記載のガス組成物において、前記苦味剤はカシン、ケブラショ、クエルセチン、キニーネ、塩酸キニーネ、硫酸キニーネ、八アセチル化スクロース、安息香酸スクロース、ナリンギン、ブルシン、硫酸ブルシン、リモニン、ゲンチアナ紫、アガリシン酸、カフェイン、および次の構造式

【数３】

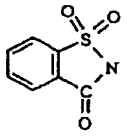


（Ⅰ）

（式中、

R^1 とR^2 は互いに同じかあるいは異なるもので、各々炭素原子数が１ないし４のアルキル基であり；R^3 はベンジル基あるいはクロロベンジル基であり；Ｘはハロゲン原子、RCO_2 （式中、Ｒは炭素原子数が１ないし６の直鎖状あるいは分鎖状のアルキル基、又はペニル基を示す）又は次の構造式

【数４】



（Ⅱ）

で表されるサッカリドを示す）で表されるｗ－ジアルキルアミノ－２，６－ジメチルアセトアニリドの第四級有機塩から成る群より選ばれる単独化合物あるいは２種以上の化合物の混合物であることを特徴とするガス組成物。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、苦味剤を含有するガス組成物に関し、より具体的には、相当に強い苦味を有する苦味剤を含有し、幻覚を生ぜしめ、人や動物が直接あるいは間接的に吸引する場合には拒否感を生ぜしめるガス組成物に関する。

【０００２】

【従来の技術】従来よりよく知られているように、ブタン（BH_4）で代表される炭化水素系ガスは、天然ガスあるいは原油の常圧蒸留工程により得られ、各種の異性体を有し、これらは単独あるいは混合された状態で用いられている。ブタン等は各種の製造業体、例えばガソリン製造分野で揮発性調節剤として広く使用されており、その他エンジン、家庭、商業用原料としても幅広く用い

られている。

【０００３】しかし、家庭、商業用原料として使用されているブタンガスの場合、スプレー缶等の容器に充填させて市販すると、一部の人々が幻覚効果を得るために吸入することがしばしば発生して、青少年の健康および社会的に大きな問題を起こしている。実際に、ブタン等を吸入した場合には、幻覚効果は勿論のこと、窒息状態を誘導する等の問題を伴うことになる。

【０００４】ブタンガスをはじめ他の天然ガスは、ガスの流出を防止するために腐臭剤と称される添加剤を必ず入れるように法規で制定されているが、現在までブタンガスの吸入を有効に防止することができる技術に対する研究はまだ進行していない。最近、嫌悪剤という添加剤をブタンガスに含有させて臭い悪臭を放出させ、ブタンガスの吸入を防止する試みがあったが、かかる嫌悪剤が一定量以上にブタンガスに添加されれば、ブタンガスを本来の目的に使用する場合にも、やはり悪臭を放出してしまうという問題があった。

【０００５】従って、幻覚効果を得るために使用されることを防止するとともに、ブタンガスを本来の目的に使用する場合には、悪臭等の使用上の不都合を生じない新規なガス組成物の開発が要求されている。

【０００６】

【発明が解決しようとする課題】従って、本発明の目的は、ガス自体の物理的、化学的性質には影響を及ぼさず、相当に強い苦味を有する苦味剤を前記ガスとともにスプレー缶等の容器に充填させ、人等が幻覚効果を得るために吸入しようとする場合には、相当強い苦味を発してその吸入を防止することができるガス組成物を提供するにある。

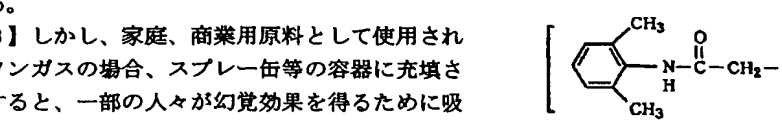
【０００７】

【課題を解決するための手段】本発明は、苦味剤を含有するガス組成物に特徴を有するものであり、以下に、本発明を更に詳細に説明する。

【０００８】本発明のガス組成物中のガスには、ブタンで代表される炭化水素系のガス、例えば炭素原子数が１ないし１０の炭化水素系のガスが全て含有され、特に吸入時に幻覚作用を引き起こす全てのガスが含まれる。

【０００９】また、本発明のガス組成物に使用することができる苦味剤の種類は特に限定されるものではなく、従来の苦味剤は全て利用することができる。例えば、カシン、ケブラショ、クエルセチン、キニーネ、塩酸キニーネ、硫酸キニーネ、ハーアセチル化スクロース、安息香酸スクロース、ナリンギン、ブルシン、硫酸ブルシン、リモニン、ゲンチアナ紫、アガリシン酸、カフェイン、および次の構造式

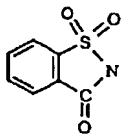
【数５】



（Ⅰ）

（式中、R^1とR^2は互いに同じかあるいは異なるもので、各々炭素原子数が１ないし４のアルキル基であり；R^3はベンジル基あるいはクロロベンジル基であり；Xはハロゲン原子、RCO_2（式中、Rは炭素原子数が１ないし６の直鎖状あるいは分鎖状のアルキル基、又はペニル基を示す）又は次の構造式

【数６】



（Ⅱ）

で表されるサッカリドを示す）で表されるｗ－ジアルキルアミノ－２，６－ジメチルアセトアニリドの第四級有機塩から成る群より選ばれる単独化合物あるいは２種以上の化合物の混合物が使用できる。

【００１０】上記に示す苦味剤は、特有の苦味を有しており、人体には全く無害なものであることが知られている（米国特許第３，０８０，３２７号、米国特許第３，２６８，５７７号および大韓民国特許出願公告第９５－３４２３号）。

【００１１】前記苦味剤は通常的に、メタノール、不凍液、繊維柔軟剤、農薬等のように人体に有害な化学製品の服用を防止する目的で主に使用されている。また、前記苦味剤はブタン等のガスに対して非活性であるので、ブタン等と混合使用しても物理的、化学的反応は生じない。

【００１２】本発明のガス組成物は、ブタンなどのガスとともに苦味剤を人為的に口や鼻を通して人体に吸入した時には、舌の感覚能力により相当の苦味が感じられるので、人が吸入した時に吐き気をもよおし、吸入を抑制することができる。

【００１３】本発明のガス組成物においては、前記苦味剤は可能な限り少ない量で充分な効果を得るようにすることが望ましいが、個人の感覚能力により一部の偏差があり、ガス組成物全体を基準として０．０５ｐｐｍ以上、望ましくは１．０ｐｐｍ以上で、且つ１０，０００ｐｐｍ以下で含有されるようにする。苦味剤の含有量が０．０５ｐｐｍ未満であると、本発明の目的である苦味による吸入防止効果を充分に発揮することができない。また１０，０００ｐｐｍより過剰で使用する場合には、ガス本来の目的である家庭、商業用熱料で使用するときに熱効率の低下等の障害要因を引き起こすばかりでなく、長期間の保管時に沈殿により種々の問題を生じ、更に経済的な側面からも望ましくない。したがって、適切量の苦味剤の添加が必要であるが、適切な添加量は苦味

剤の種類により異なり、その添加効果は苦味剤の含有量に比例して増大する。

【００１４】更に、本発明のガス組成物は、苦味剤とともに苦味剤を溶解する溶媒を含有することができるが、その目的は粒子状態の苦味剤が長時間放置されると、ガス組成物中に苦味剤が沈殿してその効果が発揮されにくくなる場合があるからである。前記溶媒は可能な限りガス組成物自体の目的に影響を及ぼさないものを選択して使用しなければならないが、特に限定されるものではない。

【００１５】本発明で使用することができる溶媒は、例えば炭素原子数が１以上の直鎖状、分鎖状あるいは環状のアルコール、アセトン、メチルエチルケトン、ベンゼン、トルエン、エチルアセテート、クロロホルム、ジクロロメタンおよびジエチルエーテルから成る群より選ばれる単独溶媒あるいは２種以上の混合溶媒である。

【００１６】前記溶媒は、ガス組成物全体を基準として０．１重量%以上、望ましくは０．２重量%、且つ１０重量%以下で含有されているようにする。この場合、溶媒の含有量が０．１重量%未満だと、本発明で要求する苦味剤の沈殿防止効果を得ることができないのみでなく、残存する粉末状の苦味剤は、ガスが噴出する容器の噴出口を塞いでしまうという問題が生じる。また１０重量%を超えて必要以上に多くの量を使用すれば、ガス本来の目的である熱料としての熱効率を低下する恐れがあるばかりでなく、経済的な側面からも望ましくない。

【００１７】上記組成からなる本発明のガス組成物は、通常的に使用されるブタン本来の物理的、化学的物性には影響を及ぼさず、一部の人々が麻薬的な効果を得るためにブタンを吸入する用途での使用を防止できる。

【００１８】

【実施例】以下、本発明を次の実施例及び比較例に基づいて詳細に説明するが、本発明は実施例によって限定されることはない。

【００１９】実施例１～１５及び比較例１～２

５２０ｍｌのスプレー缶の容器に、表１で示す組成で、ブタンガス、溶媒、苦味剤を混合してガス組成物を調製した。上記調製した各々のガス組成物を、無作為に選定した１５名の人々に各１回３秒間噴射、吸入させて個人の感知能力を以下の５種の等級に分けて、感覚程度を設問調査して評価した。感覚等級別の評価項目の内容は次のようである。

【００２０】感覚等級

Ａ：耐えにくいほどの、相当強い苦味を感ずる。

Ｂ：耐えにくいほどの、苦味を感ずる。

Ｃ：耐えられるが、相当強い苦味を感ずる。

Ｄ：耐えられるが、苦味を感ずる。

Ｅ：耐えられるし、苦味も感じない。

【００２１】

【表１】

ブタン組成物		感覚等級（単位：名）				
		A	B	C	D	E
実施例1	ブタン（100g） ゲンチアナ紫（10mg） メタノール（1ml）	−	2	10	3	−
実施例2	ブタン（100g） アガリシン酸（15mg） アセトン（1ml）	−	1	11	3	−
実施例3	ブタン（100g） キニーネ（10mg） エタノール（1ml）	−	3	7	5	−
実施例4	ブタン（100g） ナリンギン（5mg） メタノール（1ml）	−	−	9	6	−
実施例5	ブタン（100g） ケブラショ（30mg） エタノール（3ml）	3	6	5	1	−
実施例6	ブタン（100g） 硫酸キニーネ（50mg） メタノール（4ml）	5	7	3	−	−
実施例7	ブタン（100g） カシン（5mg） メチルエチルケトン（1ml）	−	2	8	5	−
実施例8	ブタン（100g） 安息香酸スクロース（8mg） ジクロロメタン（1ml）	−	4	6	5	−
実施例9	ブタン（100g） ブルシン（10mg） メタノール（1ml）	−	6	8	1	−
実施例10	ブタン（100g） 硫酸ブルシン（20mg） エタノール（2ml）	1	7	7	−	−
実施例11	ブタン（100g） ブルシン（10mg） 安息香酸ジナトニウム(1)（3mg） エタノール（1ml）	9	5	1	−	−
実施例12	ブタン（100g） 塩化ジナトニウム(2)（20mg） エタノール（3ml）	10	4	1	−	−
実施例13	ブタン（100g） 安息香酸ジナトニウム(1)（5mg） メタノール（1ml）	8	6	1	−	−
実施例14	ブタン（100g） ジナトニウムサッカリド(3)（2mg） エタノール（0.5mg）	7	7	1	−	−
実施例15	ブタン（100g） ジナトニウムサッカリド(3)（0.5mg） エタノール（1mg）	2	9	4	−	−
比較例1	ブタン（100g）	−	−	−	−	15
比較例2	ブタン（100g） エタノール（10mg）	−	−	−	−	15

（1）安息香酸ジナトニウム：R^1 とR^2 は各々エチル基、R^3 はベンジル基、Xは安息香酸塩である前記構造式（1）で示される化合物。

（2）塩化ジナトニウム：R^1 とR^2 は各々エチル基、R^3 はベンジル基、Xは塩化物である前記構造式（1）で示される化合物。

（3）ジナトニウム　サッカリド：R^1 とR^2 は各々エチル基、R^3 はベンジル基、Xはサッカリドである前記の構造式（1）で示される化合物。

【0022】

【発明の効果】本発明のガス組成物は、相当強い苦味を有するので、人が幻覚効果を得るために吸入する場合に相当の苦味を感じさせて吸入を困難とする効果を有する。

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(54) Oral pharmaceutical dosage forms with reduced potential for drug abuse, comprising respiratory irritants or bitter substances

(57) Solid oral dosage forms of controlled substances containing aversive agents are useful in reducing abuse by chewing or inhaling.

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Description

BACKGROUND

[0001] Abuse of controlled substances is a serious and growing problem throughout the world. For example, the abuse of an extended release form of oxycodone has been the recent subject of many articles such as 'Playing With Pain Killers' and 'How One Town Got Hooked'. See, Newsweek, April 9, 2001, pages 45-51. Further, The New York Times profiled the problem of oxycodone abuse by inhalation of the crushed pill. See, The New York Times, July 29, 2001. It is estimated that in America four million people over the age of 12 used prescription painkillers and stimulants for non-medical reasons in the space of just one month, approximately half of them saying they'd done it for the first time. Emergency room visits related to such abuse approximately doubled between 1992 and 1999.

[0002] There are three main routes that drug abusers use for administering the drug substances: parenteral, oral, and inhalation. The parenteral route is commonly called 'mainlining' and requires the drug substance to be in solution such that it can be injected intravenously with a syringe. For solid dosage form drugs this requires some type of extraction and concentration procedure to render the drug substance suitable for injection. Inhalation of a solid drug substance through the nose is commonly called 'snorting'. For solid dosage form drugs this requires only that the dosage form be crushed into a powder, or emptied from a capsule. Breathing in vapors is frequently known as 'huffing'. Both snorting and huffing result in the rapid absorption of the drug substance through the mucosa of the respiratory system.

[0003] The potential for abuse is increased by the use of extended release formulations because they typically contain more than the immediate release single dose of active ingredient. Circumventing the extended release mechanism delivers the full dose, which is intended to be delivered over a longer time period, immediately. For example, crushing an extended release oxycodone tablet separates a gelling matrix from the oxycodone active ingredient, such that when inhaled through the nose the gelling matrix cannot exert the extended release effect. Similarly it is sometimes possible to circumvent the extended release effect by chewing the dosage form.

[0004] The use of coatings to extend the release of drug substances is very well known in the art (Remington's Pharmaceutical Sciences, 16th Edition, Chapter 90). Such dosage forms are also subject to said modes of abuse because the coating can be damaged by crushing or chewing.

[0005] WO0108661 describes an extended release dosage form of opioids that uses an ion exchange resin. This dosage form is also subject to said modes of abuse because the ion exchange resin and the active ingredient can be separated by crushing.

[0006] Various methods have been used to reduce the potential for abuse of controlled substances. These methods have focussed on the parenteral and oral routes of administration.

[0007] US3,773,955, US3,966,940, and US4,457,933 describe oral dosage forms containing a combination of opioid agonists and antagonists, in which the effect of the antagonist when administered according to the correct procedure does not affect the therapeutic pain management value of the agonist. However, when the agonist and antagonist are extracted for parenteral administration by an addict the effect of the agonist desired by the addict is decreased. This approach was further adopted in WO9004965 where it was incorporated into a transdermal delivery device, and in US 6,228,863 where it was developed into a dosage form from which the agonist could not be separated from the antagonist except by using a sophisticated multi-step procedure.

[0008] In US 3,980,766 multiple methods for reducing abuse potential are described. One method is to include a thickening agent such that the concentrated extract containing the drug can not be injected with a syringe. Another is the incorporation of agents that cause the precipitation of the drug during isolation, thus rendering it unsuitable for injection. The addition of a thickener has also been used in US 4,070,494, WO9107950, and WO9520947.

[0009] In WO0033835 additives are included in the dosage forms such that when added to drinks create a visible change in the drink. This invention reduces the potential for abuse by oral administration of the substance by one person to another without their knowledge.

[0010] The use of bitter and sour agents to minimize the risk of ingestion of poisonous compounds is well known in the art. For example, see US 3,268,577, GB 2358585, JP 2000026260, and Chemistry and Industry (London), volume 22, 721-723, 1998). In all such cases the purpose of the bitter or sour agent is to prevent ingestion.

[0011] However, none of the cited references solve the problem of potential abuse of therapeutic compounds via inhalation or chewing. Now, Applicants have surprisingly discovered a dosage form useful in reducing the potential for drug abuse via inhalation or chewing.

[0012] The term "high," as used herein means the non-therapeutic effect desired by drug addicts and recreational drug users

[0013] The term "respiratory mucosal membrane" as used herein means the mucous membrane lining the nasal and pharyngeal cavities, the bronchial tubes, and the lungs. Typically, snorting into the nasal cavity is the common, preferred route of abuse for a solid oral dosage form which has been crushed by one intending to inhale said crushed dosage form to obtain the high.

[0014] The term "respiratory irritant' as use herein means substances that cause irritation when administered to the respiratory mucosal membrane. Said irrita-

tion can include, but is not limited to, coughing, dyspnea, rhinitis, nasal congestion, eye irritation, lachrymation, and sneezing.

[0015] When describing dosage forms the term "immediate release" as used herein means a dosage form from which the active ingredient is dissolved as quickly as possible after administration. In the pharmaceutical arts said immediate release dosage forms are frequently referred to as "conventional" dosage forms.

[0016] When describing dosage forms the term "modified release" as used herein means a dosage form whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. Said modified release dosage forms include dosage forms commonly known in the art as, delayed, sustained, extended, targeted, prolonged, pulsatile, zero-order, constant rate, and controlled.

[0017] The term "aversive response" as used herein means a response in a person, resulting from administration of a dosage form containing a controlled substance, via any of the known routes of administration, sufficiently unpleasant that said person decides not to administer said dosage form by the same route of administration again

[0018] The term "aversive agent" as used herein means any substance that is included in a dosage form that creates an aversive response.

[0019] The term "nociceptive" as used herein means a response characterized by pain. For example the term 'nociceptive efficacy' when applied to an irritant refers to the quantification of the ability of said irritant to cause pain.

SUMMARY OF THE INVENTION

[0020] The present invention relates to an oral pharmaceutical dosage form not susceptible to abuse by respiratory mucosal membrane administration comprising one or more aversive agents.

[0021] The present invention further relates to an oral pharmaceutical dosage form not susceptible to abuse by chewing comprising one or more aversive agents.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The present invention relates to an oral pharmaceutical dosage form not susceptible to abuse by respiratory mucosal membrane administration comprising one or more aversive agents.

[0023] The present invention further relates to an oral pharmaceutical dosage form not susceptible to abuse by chewing comprising one or more aversive agents.

[0024] In the practice of one embodiment of the invention, a respiratory irritant such as powdered chili peppers, or concentrated extracts of such products that contain capsaicin or capsaicin-like components, is incorporated into the solid oral dosage form of the controlled substance. When the oral dosage form is used as prescribed, i.e. swallowed whole, said irritant causes no aversive response. However, if the oral dosage form is rendered into a powder and inhaled, said irritant creates intense discomfort in the user, including coughing, dyspnea, rhinitis, nasal congestion, eye irritation, lachrymation, and sneezing. This intense discomfort has the effect of deterring people from using said inhalation route as a means of administration, i.e. it elicits an aversive response.

[0025] In the practice of another embodiment of the invention, a bitter tasting agent such as denatonium benzoate (Bitrex®) or a sour tasting agent such as citric acid , is incorporated into the solid oral dosage form of the controlled substance. When the oral dosage form is used as prescribed, i.e. swallowed whole, said bitter or sour substance causes no aversive response. However, if the oral dosage form is chewed, said bitter or sour substance creates an intensely unpleasant taste. This unpleasant taste has the effect of deterring people from chewing the dosage form, i.e. it elicits an aversive response.

[0026] The Controlled Substances Act of 1970 regulates the manufacturing, distribution, and dispensing of drugs that have abuse potential. The Drug Enforcement Agency (DEA) within the US Department of Justice is the chief agency responsible for enforcing said act. Drugs under the jurisdiction of said Act are divided into five schedules (I thru V) based on their medical utility, potential for abuse, and physical and psychological dependence. Schedule I substances have high abuse potential and no accepted medical use. Schedule II also have high abuse potential, but also have medical utility. Schedules III, IV, and V have progressively lower abuse potential.

[0027] Because the DEA rates abuse potential based on specific dosage forms it is not uncommon for a drug to be rated in multiple schedules. For example codeine appears as Schedule II, Schedule III, and Schedule IV, depending on the specific dosage form and dosage amount. To avoid duplication in the list of controlled substance below, multiple occurrences have been removed and any controlled substance that had multiple occurrences is placed in the highest abuse potential category for which is has been scheduled. For example, codeine has been included as Schedule II, but not Schedule III or Schedule IV. This is not intended to limit the scope of the invention. The utility of the Applicant's invention lies in the fact that any controlled substance, regardless of what schedule it appears on, is suitable for formulating into the Applicant's dosage form.

[0028] Controlled substances useful in the practice of the invention are those categorized by the DEA as Schedule II, III, IV, and V controlled substances.

[0029] Schedule II substances include, but are not limited to, 1-1-Phenylcyclohexylamine, 1-Piperidinocyclohexanecarbonitrile, Alfentanil, Alphaprodine, Amo-

barbital, Amphetamine, Anileridine, Benzoylecgonine, Bezitramide, Carfentanil, Coca Leaves, Cocaine, Codeine, Dextropropoxyphene, Dihydrocodeine, Diphenoxylate, Diprenorphine, Ecgonine, Ethylmorphine, Etorphine HCl, Fentanyl, Glutethimide, Hydrocodone, Hydromorphone, Isomethadone, Levo-alphacetylmethadol, Levomethorphan, Levorphanol, Meperidine, Meperidine intermediate-A, Meperidine intermediate-B, Meperidine intermediate-C, Metazocine, Methadone, Methadone intermediate, Methamphetamine, Methylphenidate, Metopon, Moramide-intermediate, Morphine, Nabilone, Opium extracts, Opium fluid extract, Opium poppy, Opium tincture, Opium, granulated, Opium, powdered, Opium, raw, Oxycodone, Oxymorphone, Pentobarbital, Phenazocine, Phencyclidine, Phenmetrazine, Phenylacetone, Piminodine, Poppy Straw, Poppy Straw Concentrate, Racemethorphan, Racemorphan, Remifentanil, Secobarbital, Sufentanil, Thebaine

[0030] Schedule III substances include, but are not limited to, Amobarbital, Anabolic steroids, Aprobarbital, Barbituric acid derivative, Benzphetamine, Boldenone, Butabarbital, Butalbital, Chlorhexadol, Chlorotestosterone, Chlorphentermine, Clortermine, Clostebol, Codeine, Dehydrochlormethyltestosterone, Dihydrocodeine, Dihydrotestosterone, Dronabinol, Drostanolone, Ethylestrenol, Ethylmorphine, Fluoxymesterone, Formebolone, Hydrocodone, Ketamine, Lysergic acid, Lysergic acid amide, Mesterolone, Methandienone, Methandranone, Methandriol, Methandrostenolone, Methenolone, Methyltestosterone, Methyprylon, Mibolerone, Morphine, Nalorphine, Nandrolone, Norethandrolone, Oxandrolone, Oxymesterone, Oxymetholone, Pentobarbital, Phendimetrazine, Secobarbital, Stanolone, Stanozolol, Sulfondiethylmethane, Sulfonethylmethane, Sulfonmethane, Talbutal, Testolactone, Testosterone, Thiamylal, Thiopental, Tiletamine, Trenbolone, Vinbarbital.

[0031] Schedule IV substances include, but are not limited to, Alprazolam, Barbital, Bromazepam, Butorphanol, Camazepam, Cathine, Chloral betaine, Chloral hydrate, Chlordiazepoxide, Clobazam, Clonazepam, Clorazepate, Clotiazepam, Cloxazolam, Cocaine, Delorazepam, Dexfenfluramine, Dextropropoxyphene, Diazepam, Diethylpropion, Difenoxin, Estazolam, Ethchlorvynol, Ethinamate, Ethyl loflazepate, Fencamfamin, Fenfluramine, Fenproporex, Fludiazepam, Flunitrazepam, Flurazepam, Halazepam, Haloxazolam, Ketazolam, Loprazolam, Lorazepam, Lormetazepam, Mazindol, Mebutamate, Medazepam, Mefenorex, Meprobamate, Methohexital, Methylphenobarbital, Midazolam, Modafinil, Nimetazepam, Nitrazepam, Nordiazepam, Oxazepam, Oxazolam, Paraldehyde, Pemoline, Pentazocine, Petrichloral, Phenobarbital, Phentermine, Pinazepam, Pipradrol, Prazepam, Quazepam, Sibutramine, Temazepam, Tetrazepam, Triazolam, Zaleplon, Zolpidem

[0032] Schedule V substances include, but are not limited to Buprenorphine, Difenoxin, Dihydrocodeine, Diphenoxylate, Pyrovalerone.

[0033] Preferred controlled substances useful in the practice of the invention are those categorized by the DEA as Schedule II, III, and IV controlled substances.

[0034] More preferred controlled substance useful in the practice of the invention are those categorized by the DEA as Schedule II and III controlled substances.

[0035] Most preferred controlled substance useful in the practice of the invention are those categorized by the DEA as Schedule II controlled substances. The most preferred Schedule II substance is oxycodone.

[0036] Aversive agents useful in the practice of this invention include, but are not limited to, respiratory irritants, bitter substances, and sour substances.

[0037] Aversive agents useful in the practice of this invention are solids. Said solid can be said agent in pure form or a solid containing said agent.

[0038] Aversive agents useful in the practice of this invention are of natural or synthetic origin.

[0039] An important aspect of this invention is the use of capsaicinoids as an aversive agent which acts as a respiratory irritant to create an aversive response. Capsaicinoids are alkaloid substances which occur naturally in the fruit of various chile pepper plants. The principal capsaicinoids found in most pepper plants are capsaicin, dihydrocapsaicin, capsico, and capsacutin. The principal capsaicinoid is capsaicin. There can be multiple capsaicinoids in one pepper and different peppers have different concentrations of capsaicinoids. The production of capsaicinoids is a form of chemical defense against being eaten and thus acts naturally as an animal repellant. See, Smith, R. L., Ecology and Field Biology, p. 562 (3d Ed. 1980). Capsaicinoids are the chemicals responsible for the "hot" sensation associated with peppers. The hotness of the various capsicums is directly attributable to their capsaicinoid content. Capsaicinoids generate a spicy flavor in the mouth but are irritants when applied to mucous membranes.

[0040] Capsicum is the formal term used to refer to the dried ripe fruit of the various species of chili peppers.

[0041] Therapeutically, capsaicin is listed as a counterirritant (Merck Index, 9th Ed., p. 224). Capsicum has Generally Regarded as Safe (GRAS) status in the USA. Capsaicin, capsicum, and capsicum oleoresin have monographs in the US Pharmacopeia 24.

[0042] Respiratory irritants useful in the practice of this invention include, but are not limited to, pure compounds and mixtures of capsaicin, capsico, capsacutin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, capsaicinoids, gingerol, chemical mace, piperine, isochavicine, isopiperine, piperidine, chavicine, piperettine, zingerone, shogaol, valleral, isovallerals, vanyllylamide, nonoyl vanyllamide, vanyllylamide derivatives, synthetic derivatives of capsaicinoids, and extracts, capsicums, and powders of, Capsicum frutescens varieties, Capsicum anuum varieties, Capsicum chinense varieties, Capsicum baccatum varieties, Capsicum pubescens varieties, Capsi-

cum species, Piper migrum varieties, Piper longum varieties, Piper retrofractum varieties, Piper officinarum varieties, Piperaceae species, Brassica juncea varieties, Brassica. nigra varieties, Sinapis alba varieties, Sinapis arvensis varieties, Zingiber officinale varieties, and Lactarius vellereus varieties and mixtures thereof.

[0043] Preferred respiratory irritants useful in the practice of the invention are pure compounds and mixtures of capsaicin, capsico, capsacutin, dihydrocapsaicin, nordihydrocapsaicin,homocapsaicin, homodihydrocapsaicin, capsaicinoids, gingerol, chemical mace, piperine, isochavicine, isopiperine, piperidine, chavicine, piperettine, zingerone, shogaol, valleral, isovallerals, vanyllylamide, nonoyl vanyllamide, vanyllylamide derivatives, synthetic derivatives of capsaicinoids, and extracts, capsicums, and powders of, Capsicum frutescens varieties, Capsicum anuum varieties, Capsicum chinense varieties, Piper migrum varieties, Piper longum varieties, Piper retrofractum varieties, Piper officinarum varieties, Brassica juncea varieties, Brassica. nigra varieties, Sinapis alba varieties, Sinapis arvensis varieties, and Zingiber officinale varieties and mixtures thereof.

[0044] More preferred respiratory irritants useful in the practice of the invention are pure compounds and mixtures of capsaicin, capsico, capsacutin dihydrocapsaicin, nordihydrocapsaicin,homocapsaicin, homodihydrocapsaicin, capsaicinoids, gingerol, piperine, isopiperine, piperidine, piperettine, zingerone, shogaol, valleral, isovallerals, vanyllylamide, vanyllylamide derivatives, and extracts, capsicums, and powders of, Capsicum frutescens varieties, Capsicum anuum varieties, Capsicum chinense varieties, Piper migrum varieties, Piper longum varieties, Piper retrofractum varieties, Piper officinarum varieties, Brassica juncea varieties, Brassica. nigra varieties, Sinapis alba varieties, Sinapis arvensis varieties, and Zingiber officinale varieties and mixtures thereof.

[0045] Most preferred respiratory irritants useful in the practice of the invention are pure compounds and mixtures of capsaicin, capsacutin dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, capsaicinoids, gingerol, piperine, isopiperine, zingerone, shogaol, and vanyllylamide derivatives and mixtures thereof.

[0046] The use of capsaicin with cocaine is contraindicated.

[0047] The amount of respiratory irritant useful in the practice of this invention is that which is sufficient to elicit an aversive response in the user when said irritant is inhaled through the respiratory mucosa but that which is not sufficient to elicit an aversive response or an adverse medical response in the user when said irritant is swallowed as a solid oral dosage form in the manner prescribed.

[0048] The nociceptive efficacy of the respiratory irritants varies greatly depending both on chemical structure of the active ingredient of said irritant, and the amount of active ingredient in said irritant. The following amounts of respiratory irritants are provided as examples. Effective amounts of other respiratory irritants can be determined using techniques well known to those skilled in the art.

[0049] The preferred amount of the respiratory irritants capsaicin and dihydrocapsaicin is a combined total of 0.002-100mg per dose.

[0050] The preferred amount of the respiratory irritant zingerone is 0.04-200mg per dose.

[0051] The preferred amount of the respiratory irritant shogaol is 0.04-200mg per dose

[0052] The preferred amount of the respiratory irritant piperine is 0.04-200mg per dose

[0053] The preferred amount of the respiratory irritants capsicums of Capsicum annum, Capsicum frutescens, and Capsicum chinense is 0.1 - 450mg per dose.

[0054] The more preferred amount of the respiratory irritants capsaicin and dihydrocapsiacin is a combined total of 0.004-25mg per dose.

[0055] The more preferred amount of the respiratory irritant zingerone 0.2-150mg per dose.

[0056] The more preferred amount of the respiratory irritant shogaol 0.2-150mg per dose

[0057] The more preferred amount of the respiratory irritant piperine is 0.2-150mg per dose

[0058] The more preferred amount of the respiratory irritants capsicums of Capsicum annum, Capsicum frutescens, and Capsicum chinense is 0.4-350mg per dose

[0059] The most preferred amount of the respiratory irritants capsaicin and dihydrocapsiacin is a combined total of 0.02-15mg per dose.

[0060] The most preferred amount of the respiratory irritant zingerone 0.2-100mg per dose.

[0061] The most preferred amount of the respiratory irritant shogaol 0.2-100mg per dose

[0062] The most preferred amount of the respiratory irritant piperine is 0.2-100mg per dose

[0063] The most preferred amount of the respiratory irritants capsicums of Capsicum annum, Capsicum frutescens, and Capsicum chinense is 0.6-250mg per dose

[0064] Bitter agents also create an aversive response. The use of bitter agents is particularly useful in preventing abuse of controlled substances by chewing the oral dosage form. Bitter agents useful in the practice of this invention include, but are not limited to, agaricic acid, benzyl acetate, brucine, brucine sulfate, caffeine, capsaicin, catechin, dadzein, denatonium benzoate (Bitrex®) and other denatonium salts, denatonium capsaicinate, denatonium chloride, denatonium saccharide, diethyl phthalate, epicatechin, genistein, gentian violet, gerianol, hydroxytyrosol, kashin, limonin, linalool, linalool acetate, methyl anthranilate, naringin, nobiletin, oleuropin, phenylethyl alcohol, polyphenols, quassin, quebracho, quercitin, quinine, quinine sulfate, quinine hydrochloride, sinensetin, sucrose benzoate, sucrose

octaacetate, and tangeretin and mixtures thereof.

[0065] Preferred bitter agents useful in the practice of this invention are, denatonium benzoate (Bitrex®) and other denatonium salts, denatonium capsaicinate, denatonium chloride, denatonium saccharide, limonin, linalool, linalool acetate, naringin, quassin, quercitin, sucrose benzoate, and sucrose octaacetate and mixtures thereof.

[0066] Most preferred bitter agents useful in the practice of this invention are denatonium benzoate (Bitrex®), denatonium capsaicinate, denatonium saccharide, and sucrose octaacetate and mixtures thereof.

[0067] Further, sour agents also create an aversive response. The use of sour agents is particularly useful in preventing abuse of controlled substances by chewing the oral dosage form. Sour agents useful in the practice of this invention include, but are not limited to, acidic organic compounds that contain one or more acidic protons per molecule and mixtures thereof.

[0068] Preferred sour agent useful in the practice of the invention are acidic organic compounds that contain two or more acidic protons per molecule and mixtures thereof.

[0069] Most preferred sour agents useful in the practice of the invention are citric acid and tartaric acid and mixtures thereof.

[0070] The controlled substance and aversive agent are incorporated into the dosage form using any of the methods known in the art for preparation of solid oral dosage forms. See, Remington's Pharmaceutical Sciences, 16th Edition.

[0071] Further, different combinations of aversive agents can be combined in the same dosage form. For example, if it is desired to reduce the potential for abuse via both inhalation and chewing, it may be desirable to combine both a respiratory irritant and a bitter agent in the same formulation. Further, combination of avervise agents can sometime have a synergistic effect, such that the combination has a greater effect than the sum of the individuals taken separately. Still further, people have different responses to taste, such that a mixture of bitter agents may be needed to be effective in a larger fraction of the population.

[0072] In addition to the controlled substance and aversive agent, excipients are used in the manufacture of the oral dosage forms of the present invention. Excipients useful in the practice if this invention include but are not limited to preservatives, viscosity agents, fillers, lubricants, glidants, disintegrants, binders, and encapsulants.

[0073] Preferred preservatives include, but are not limited to, phenol, alkyl esters of parahydroxybenzoic acid, o-phenylphenol benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chlorobutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred are the salts of benzoic acid, cetylpyridinium chloride, methyl paraben and propyl paraben. The compositions of the present invention generally include from 0-2% preservatives.

[0074] Preferred viscosity agents include, but are not limited to, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl-methylcellulose, hydroxypropylcellulose, sodium alginate, carbomer, povidone, acacia, guar gum, xanthan gum and tragacanth. Particularly preferred are methylcellulose, carbomer, xanthan gum, guar gum, povidone, sodium carboxymethylcellulose, and magnesium aluminum silicate. Compositions of the present invention include 0-25% viscosity agents.

[0075] Preferred fillers include, but are not limited to, lactose, mannitol, sorbitol, tribasic calcium phosphate, dibasic calcium phosphate, compressible sugar, starch, calcium sulfate, dextro and microcrystalline cellulose. The compositions of the present invention contain from 0-75% fillers.

[0076] Preferred lubricants include, but are not limited to, magnesium stearate, stearic acid, and talc. The pharmaceutical compositions of the present invention include 0-2% lubricants.

[0077] Preferred glidants include, but are not limited to, talc and colloidal silica. The compositions of the present invention include from 0-5% glidants.

[0078] Preferred disintegrants include, but are not limited to, starch, sodium starch glycolate, crospovidone, croscarmelose sodium, polacrilin potassium, and microcrystalline cellulose. The pharmaceutical compositions of the present invention include from 0-30% disintegrants.

[0079] Preferred binders include, but are not limited to, acacia, tragacanth, hydroxypropylcellulose, pregelatinized starch, gelatin, povidone, hydroxypropylcellulose, hydroxypropyl-methylcellulose, methylcellulose, sugar solutions, such as sucrose and sorbitol, and ethylcellulose. The compositions of the present invention include 0.1-10% binders.

[0080] Encapsulants useful in the practice of the present invention include, but are not limited to permable coatings, impermeable coatings, and matrices.

[0081] Permeable coatings useful in this invention are well know to one skilled in the art and include Eudragit® RL, and Eudragit® RS (Rohm-Pharma Darmstadt, Germany)

[0082] Non-permeable coatings useful in this invention are well known to one skilled in the art and include Aquacoat CPD (FMC Corporation, Philadelphia, PA, USA), Eudragit® E100, Eudragit® L100, Eudragit® S100 (Rohm-Pharma Darmstadt, Germany), Kollicoat® MA 30 DP (BASF Aktiengesellschaft, Ludwigshafen, Germany), Opadry light pink.

[0083] Plastizers for use with coatings useful in the practice of the invention include but are not limited to, triethyl citrate, 1,2-propylene glycol, polyethylene glycols, and tracetin.

[0084] Matrices for encapsulation useful in the prac-

tice of the invention include, but are not limited to, anion exchange resins, cation exchange resins, polymeric adsorbents, carbonaceous adsorbents, cellulosic polymers, and acrylic polymers.

[0085] Dosage forms of the present invention are immediate release or modified release.

[0086] The following non limiting examples illustrate the present invention:

EXAMPLE 1 30mg Extended release oxycodone tablets using capsaicin

[0087]

Ingredient	mg/tabl et
Oxycodone HCl	30
Lactose	200
Eudragit® RS PM	45
Purified water	as needed
Stearyl alcohol	75
Talc	7.5
Magnesium stearate	3.75
Capsaicin	13.75

[0088] The required quantities of oxycodone hydrochloride, a Schedule II controlled substance, spray-dried lactose, capsaicin, and Eudragit® RS PM are placed into an appropriately-sized mixer, and mixed for approximately 5 minutes. While the powders are mixing, the mixture is granulated with enough water to produce a moist granular mass. The granules are then dried in a fluid bed dryer at 60° C., and then passed through an 8-mesh screen. Thereafter, the granules are redried and pushed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60-70° C., and while the granules are mixing, the melted stearyl alcohol is added. The warm granules are returned to the mixer.

[0089] The coated granules are removed from the mixer and allowed to cool. The granules are then passed through a 12-mesh screen. The granulate is then lubricated by mixing the required quantity of talc and magnesium stearate in a suitable blender. Tablets are compressed to 375 mg in weight on a suitable tableting machine.

EXAMPLE 2 30mg Extended release morphine sulfate tablets using capsaicin

[0090]

Ingredient	mg/tabl et
Morphine sulfate	30
Lactose	79.5
Eudragit® RL	12
Stearyl aclohol	24
Talc	3
Magnesium stearate	1.5
Capsaicin	10

[0091] These tablets are prepared according to the following method:

[0092] Morphine sulfate, a Schedule II controlled substance, capsaicin, and lactose are intimately mixed in a suitable mixer. A granulation is then prepared by incorporating the granulating fluid into the mixing powders using Eudragit® RL. The granulate is then dried and passed through a 12 mesh screen. The stearyl alcohol is melted and incorporated into the warm granules using a suitable mixer. After cooling, the granules are passed through a 12 mesh screen. The granules are then lubricated by mixing in the talc and stearyl alcohol. Tablets are then compressed on a suitable tabletting machine using round biconvex tooling 10/32" in diameter.

EXAMPLE 3 8mg extended release Hydromorphone capsules using shogaol

[0093]

Ingredient	mg/capsu le
Loading	
Hydromorphone HCl	8
Opadry light pink (Y-5-1442)	4
Purified water	as needed
18/20 mesh sugar spheres	148
Overcoating	
Opadry light pink (Y-5-1442)	8.4
Purified water	as needed
Retardant coating	
Eudragit® RS 30D	7.6
Eudragit® RL 30D	0.8

(continued)

Ingredient	mg/capsu le
Retardant coating	
Triethyl citrate	1.68
Talc	3.36
Purified water	as needed
Second overcoat	
Opadry light pink (Y-5-1442)	9.6
Purified water	ass needed
Encapsulation	
Size #2 clear hard gelatin capsules	
Shogaol	75

[0094] Hydromorphone beads are prepared by dissolving hydromorphone HCl, a Schedule II controlled substance, in water, adding Opadry Y-5-1442 and mixing for about 1 hour to obtain a 20% w/w suspension. This suspension is then sprayed onto Nu-Pareil® 18/20 mesh beads using a Wurster insert.

First Overcoat

[0095] The loaded hydromorphone beads are then overcoated with a 5% w/w gain of Opadry Light Pink using a Wurster insert. This overcoat is applied as a protective coating.

Retardant Coat

[0096] After the first overcoat, the hydromorphone beads are then coated with a 5% weight gain of a retardant coating mixture of Eudragit® RS 30D and Eudragit® RL 30D at a ratio of 90:10, RS to RL. The addition of Triethyl Citrate and Talc is also included in the Eudragit suspension. The Wurster insert is used to apply the coating suspension.

Second Overcoat

[0097] Once the retardant coating is complete, the hydromorphone beads are given a final overcoat of Opadry Light Pink to a 5% weight gain using a Wurster insert. This overcoat is also applied as a protective coating.

Curing

[0098] After the completion of the final overcoat, the hydromorphone beads are cured in a 45° C. oven for 2 days.

Encapsulation

[0099] The beads are mixed with shogaol in a suitable mixer and the mixture is then hand filled in size #2 clear gelatin capsules.

EXAMPLE 4 30 mg extended release oxycodone tablets using piperine

[0100] Tablets are prepared as described in Example 1, except that the respiratory irritiant used is piperine, and the quantities used are as follows:

Ingredient	mg/tabl et
Oxycodone HCl	30
Lactose	138.75
Eudragit® RS PM	45
Purified water	as needed
Stearyl alcohol	75
Talc	7.5
Magnesium stearate	3.75
Piperine	75

EXAMPLE 5 30mg Extended release morphine sulfate tablets using denatonium benzoate

[0101] These tablets are prepared as described in Example 2 except that the capsaicin is replaced with 2mg/tablet of denatonium bezoate (available as Bitrex® from Macfarlan Smith, Edinburgh, UK).

EXAMPLE 6

[0102] A Caucasian female, age 27 , weighing 50 kg suffering from back pain takes a 30mg tablet of sustained release oxycodone from Example 1 as prescribed, by swallowing said tablet whole. She experiences 15 hours of pain relief without any aversive response.

EXAMPLE 7

[0103] A Caucasian male recreational drug user, age 45, weighing 80 kg crushes a 30mg tablet of sustained release oxycodone from Example 1 to give a powder. He then inhales said powder through the nose. He immediately experiences an aversive response, including an intense burning sensation in the nasal passages, sneezing, watery eyes and headache.

EXAMPLE 8

[0104] An African-American male, aged 18, weighing 66 kg, who has never abused drugs crushes an extend-

ed release 30mg morphine tablet from Example 2 into a powder and then inhales said powder through the nose. He immediately experiences an aversive response, including an intense burning sensation in the nasal passages, coughing, and watery eyes.

EXAMPLE 9

[0105] An Asian female, recreational drug user, aged 28, weighing 55 kg, breaks an 8mg hydromorhone capsule from Example 3 and empties out the contents from the capsule. She crushes the beads into a fine powder and then inhales said powder through the nose. She immediately experiences an aversive response, including an intense burning sensation in the nasal passages and the throat, coughing, and watery eyes.

EXAMPLE 10

[0106] At a party a Caucasian male recreational drug user, aged 17, weighing 65 kg is offered a 30mg morphine sulfate tablet, as prepared in Example 5 . He chews it and he immediately experiences an aversive response causing him to spit out the chewed dosage form.

Claims

1. An oral pharmaceutical dosage form not susceptible to abuse by respiratory mucosal membrane administration comprising one or more aversive agents.

2. An oral pharmaceutical dosage form not susceptible to abuse by chewing comprising one or more aversive agents.

3. An oral pharmaceutical dosage form not susceptible to abuse by respiratory mucosal membrane administration comprising one or more aversive agents and a controlled substance.

4. An oral pharmaceutical dosage form not susceptible to abuse by chewing comprising one or more aversive agents and a controlled substance.

5. An oral pharmaceutical dosage form according to Claim 3, wherein said aversive agent is a respiratory irritant selected from the group consisting of capsaicin, capsacutin dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, capsaicinoids, gingerol, pipeline, isopiperine, zingerone, shogaol, and vanyllylamide derivatives, and mixtures thereof.

6. An oral pharmaceutical dosage form according to Claim 4, wherein said aversive agent is a bitter substance selected from the group consisting of denatonium benzoate, denatonium capsaicinate, denatonium chloride, denatonium saccharide, limonin, linalool, linalool acetate, naringin, quassin, quercitin, sucrose benzoate, and sucrose octaacetate, and mixtures thereof.

7. An oral pharmaceutical dosage form according to Claim 5, wherein said controlled substance is selected from the group consisting of Schedule II, III, IV, and V controlled substances.

8. An oral pharmaceutical dosage form according to Claim 6, wherein said controlled substance is selected from the group consisting of Schedule II, III, IV, and V controlled substances.

9. An oral pharmaceutical dosage form according to Claim 7, wherein said controlled substance is a Schedule II controlled substance.

10. An oral pharmaceutical dosage form according to Claim 8, wherein said controlled substance is a Schedule II controlled substance.

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 02 25 6157

Claim(s) searched completely:
-

Claim(s) searched incompletely:
1-10

Reason for the limitation of the search:

1) Present claims 1-4 relate to dosage forms comprising "one or more aversive agents". This expression is considered to be vague and unclear in the sense of Article 84 EPC to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely the substances indicated in claims 5 and 6.

2)The expressions "controlled substance" as well as "Schedule II, III, IV and V controlled substances" in claims 3-10 are regarded as leading to a lack of clarity within the meaning of Article 84 EPC, since these terms do not necessarily have the same meaning in other countries than the US. In addition, the applicant's attention is drawn to the fact that some compounds may be already known for their abuse potential, but are as yet not identified as "controlled substances". Consequently, the search has been restricted to oral pharmaceutical dosage forms comprising an active agent consisting of hydromorphone, oxycodone, methadone or morphine (mentioned at p.6, l.190 and in examples 1-10 of the description).

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 6157

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X	GB 2 331 702 A (VENALINK LTD) 2 June 1999 (1999-06-02) * page 1, line 10 - line 11 * * page 1, line 16 - line 17 * * page 3, line 6 - line 7 * * example * * claims 1,5,8 *	2,4,6,8, 10	
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82